REMARKS

I. The Rejection Under 35 U.S.C. § 112, First Paragraph for Lack of Written Description Should be Withdrawn

Claims 84-107 are rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. The Examiner asserts that the claimed subject matter is not described in the specification in a way as to reasonably to convey to one skilled in the art that the inventors were in possession of the claimed invention at the time of filing.

Support for the Claimed Genus

Amended claim 84 is directed to a method of assaying for modulators of β-secretase activity using a substrate that comprises a peptide having the formula P_2P_1-$P_{1'}P_{2'}$ wherein P_2 is N, P_1 is F, $P_{1'}$ is E and $P_{2'}$ is A.

Experimental results in the specification indicates that larger substrates having additional amino terminal amino acid sequence, as recited in the amended claims, are preferred because they exhibit enhanced cleavage rates (*see, e.g.,* results in Table 5 and on page 25, lines 18-20 of the specification). Furthermore, the specification specifically demonstrates the functionality of peptide substrates that comprise the residue N at the P_2 position; substrates that comprise the residue F at the P_1 position; and substrates that comprise the residue E at the $P_{1'}$ position (*see, e.g.,* Table 1 on pages 17-18, Table 2 on page 20, Table 3 on page 21 and Table 4 on page 24). Moreover polypeptides having predicted *β*-secretase cleavage sites that are analyzed by the inventors in Table 1 on pages 17-18, exemplify substrates having residue A at position $P_{2'}$ *e.g.* wild type APP (SEQ ID NO: 20) and Swedish mutations (SEQ ID NOS: 19 and 21).

References Cited by the Examiner

The Examiner continues to cite a number of references that were published after the filing date of the present patent application in order to illustrate the state of the art: Gruninger-Leitch *et al.* (*J. Biol. Chem.,* 277:4687-4693, 2002), Majer *et al.* (*Protein Science* 6: 1458-1466, 1997), Sauder *et al.* (*J. Mol. Biol.,* 300:241-248, 2000), Shi *et al.* (*J.*

Alzheimer's Disease 7: 139-148, 2005), and Tomasselli *et al.* (*J. Neurochem.,* 84:1006-1017, 2003).

Gruninger-Leitch *et al.*

The Examiner points to Gruninger-Leitch *et al.* as providing information about the state of the art at the time the application was filed, although it was published after the filing date. The authors of Gruninger-Leitch *et al.* used an experimental approach that is similar to that of the inventors, which generated amino acid substitutions at cleavage site proximal residues to address the substrate specificity of β-secretase (BACE). Additionally, cleavage of peptides from several random peptide libraries was examined to determine possible amino acid substitutions at various positions. In particular, the Examiner points out that Gruninger-Leitch *et al.* show that a single point mutation at the $P_{1'}$ or P_4 of the Swedish mutant cleavage site results in a drop in the rate of cleavage of the peptide substrate; nonetheless, the mutated substrates remained cleavable (see, Table 1 on page 4689). Essentially, what the studies presented in Gruninger-Leitch *et al.* show is that "BACE accepts a wide variety of peptidic substrates and, in contrast to other mammalian aspartic proteases, prefers acidic or polar residues at the P2 and P1' positions . . ." (page 4692, first column). This finding is consistent with the disclosure and confirms the studies of the specification and suggests that the vast majority of the peptide substrates disclosed in Table 6 of the patent application will be cleaved by β-secretase.

Majer *et al.*

The Examiner also cited Majer *et al.* 1997 indicating that Majer *et al.* shows evidence that residues further from the β-secretase cleavage site (*e.g.,* other than P_2P_1- $P_{1'}P_{2'}$) also contribute to the cleavability of the substrate (Page 8 of the Office Action). However, Majer *et al.* describes the development of inhibitors of the aspartyl protease cathepsin D based on site specificity. The amino acid substitutions described by Majer *et al.* concern the Pepstatin A peptide inhibitor compound. Therefore, the enzymatic activity measured in Majer *et al.* is inhibitory potency rather than cleavage by the protease. Because Majer *et al.* does not study protease substrates and also does not concern β-secretase, this reference does not provide any probative information regarding peptide substrates disclosed and claimed in the present application.

Sauder *et al.*

Sauder *et al.*, a reference cited by the Examiner, illustrates the interaction of a peptide substrate and an aspartyl protease at the enzymatic cleavages cite. Figure 4 of Sauder shows a six amino acid peptide centered at the cleavage site that spans the BACE binding/cleavage pocket. The figure further indicates residues of BACE that interact with the P_2-$P_{2'}$ positions which illustrates why these residues are far more important to proteolytic cleavage as compared to residues at positions more distant to the cleavage site. Thus, Sauder *et al.* provides evidence that the specification adequately supports the structure of the claimed substrates by focusing on the P_2 P_1 $P_{1'}$$P_{2'}$ amino acids. However, the application gives guidance for the structure at more distant resides as well.

Tomasselli *et al.*

Tomasselli *et al.* provides studies that support the disclosure in the specification and show that the defined genera of peptide substrates are cleaved by β-secretase (*see, e.g.*, Table 1 on page 1010). Tomaselli *et al.*, also supports the conclusion that the addition of additional residues N- or C-terminal to the core sequence of substrate can enhance cleavage activity.

Shi *et al.*

Shi *et al.* was published after the filing of the patent applications and provides further analyses regarding the cleavage of various β-secretase substrates. The authors of Shi *et al.* focused on amino acid substitutions at the P_2-$P_{2'}$ positions (see Table 2 at page 142). Of the 24 peptides tested for cleavage activity, all but two were cleaved by β-secretase with equal or greater efficiency as compared to the wt-APP sequence. The studies in Shi *et al.* further confirm that the P_2-$P_{2'}$ positions of substrate peptides are the important for cleavage efficiency and that broad range of substitutions can be made with out compromising the ability of a substrate to be cleaved. Specifically, Shi *et al.* concludes that "results of this present investigation further indicate that BACE1 can accept a wide variety of amino acid residues at the β-scissile-bond of its substrate both *in vitro* and in cells," (page 146, second column, second paragraph). The conclusions that were reached by Shi *et al.* further confirm

that the inventor's disclosure regarding the β-secretase substrates was sufficient to support the claims that are pending in the applications under examination.

Conclusion

Therefore, the art cited by the Examiner provides evidence that the claimed genus of substrates is adequately supported by the specification. In view of the foregoing amendment and remarks, the claims satisfy the written description requirement and the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

II. Double Patenting

Claims 84-108 and 110 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting in view of co-pending application nos. 10/801,487, 10/801,938 and 10/801,509. Applicants request that all provisional double patenting rejections be deferred until such time as there is an indication that subject matter is otherwise allowable in one of the pending applications. The applicants will cancel claims or file terminal disclaimers if necessary to obviate a double patenting rejection.

CONCLUSION

In view of the foregoing amendment and remarks, the Applicants believe pending claims 84, 85, 88-91, 94-108 and 110 are in condition for allowance. Applicants respectfully request reconsideration and withdrawal of all rejections and allowance of the claims currently under examination.

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Respectfully submitted,

Electronic signature: /Sharon M. Sintich/
Sharon M. Sintich
Registration No.: 48,484
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant